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TITLE: Estrogens, Genetic Polymorphins and Breast Cancer Risk

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13. ABSTRACT (Maximum 200 Words) Although the precise cause of most breast cancer cases is unknown, much attention has been focused on the role of estrogen metabolism in mammary carcinogenesis. Aromatase, estrogen hydroxylase, and catechol-O-methyltransferase are key steps in the three major enzyme systems involved in the biosynthesis and degradation of estrogen. We hypothesize that polymorphisms in genes encoding these three enzymes are associated with breast cancer risk in Nigerian women. Specific Aims: 1. To determine the presence of polymorphisms in genes encoding aromatase, estrogen hydroxylase, and catechol-O-methyltransferase in Nigerian women with breast cancer; 2. To determine the role of polymorphisms in these genes in the susceptibility to breast cancer; 3. To compare our findings with that in African American women and Caucasians. Cases will be 250 women with confirmed breast cancer recruited from hospitals in Midwestern and Southeastern Nigeria. Population-based age-matched controls without hormonal disease or cancerous lesions will be recruited from the same environment as cases. Genotyping will be conducted at the University of Pittsburgh. Our long term goal is to increase our understanding of the etiology of breast cancer, and to reduce the burden of breast cancer by identifying susceptible women for earlier diagnosis and appropriate preventive measures and treatment.			
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Annual Summary Report for Award Number DAMD17-02-1-0551**Introduction**

The study titled "Estrogens, Genetic Polymorphisms and Breast Cancer Risk" (Award Number: DAMD17-02-1-0551) was awarded to University of Pittsburgh Cancer Institute (UPCI) in Fiscal Year 2001 Department of Defense Breast Cancer Research Program (BCRP) of the U.S. Army Medical Research and Materiel Command's Office of the congressionally Directed Medical Research Programs (CDMRP). The grant was awarded as a post-doctoral training grant with Michael N. Okobia as the trainee (Principal Investigator) and Clareann H. Bunker, Ph.D an Associate Professor in the Department of Epidemiology, University of Pittsburgh, as the Co-Principal Investigator. Other Co-Investigators from University of Pittsburgh include Lewis H. Kuller, MD, Dr.P.H.; and Robert E. Ferrell, Ph.D. The Nigerian Co-Investigators are Stanley N.C. Anyanwu, MBBS, FWACS, FMCS; Emmanuel R. Ezeome, MBBS, FWACS, and Emmanuel E.O. Uche, MD, SCGS, Ph.D, FWACS.

The study was designed to investigate the presence of polymorphisms in three major genes involved in estrogen metabolism and the role of any detected polymorphisms in these genes in breast cancer susceptibility among Nigerian women. A case-control design recruiting 250 women with proven breast cancer and 250 age-matched controls without breast cancer was adopted for the study.

Body

The study was designed to be conducted over a period of three years, from July 2002 and June 2005. The study commenced in July 2002 after completion of contractual agreements between of Department of Defense (DOD) and University of Pittsburgh Cancer Institute. I arrived Nigeria in September 2002 for the first phase of the study which involves recruitment of study participants. The first three months of the study was spent holding consultations with Co-Investigators and management of the four participating institutions in Nigeria (University of Benin Teaching Hospital (UBTH), Benin City; Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi; University of Nigeria Teaching Hospital (UNTH), Enugu; and University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt. Date of meeting in each of the study sites are shown below:

University of Benin Teaching Hospital, Benin City – September 3, 2002.

Nnamdi Azikiwe University Teaching Hospital, Nnewi – September 10, 2002.

University of Nigeria Teaching Hospital, Enugu – September, 17, 2002.

University of Port Harcourt Teaching Hospital, Port Harcourt – September 24, 2002.

During the meetings in each of the study sites, we deliberated on key issues in respect of recruitment of study participants. Arrangements were made to give appointments to eligible study participants within a week in the month when the principal investigator will be around so that specimens collected from study participants could be moved to the storage site in Benin City. After consultations with the various study sites, a timetable was drawn up covering the period for recruitment of study participants.

After the initial arrangements and negotiations, there was some delay for about three months before we could begin recruiting study participants. The delay arose as a result of technical issues associated with arrangements for storage facilities for biological specimens in Nigeria. Recruitment of study participants actually commenced in December 2002 as shown in the schedule above.

Below is the schedule of visits to the Nigeria study sites

MONTH	DATE	STUDY SITE
December 2002	12/12/02 – 30/12/02	University of Benin Teaching Hospital (UBTH), Benin City
January 2003	05/01/03 – 08/01/03	Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi
"	12/01/03 – 15/01/03	University of Nigeria Teaching Hospital (UNTH), Enugu
"	19/01/03 – 22/01/03	University of Port-Harcourt Teaching Hospital (UPTH), Port Harcourt
"	27/01/03 – 29/01/03	UBTH
February 2003	02/02/03 – 05/02/03	UPTH
"	10/02/03 – 14/02/03	UBTH
"	17/02/03 – 19/02/03	NAUTH
"	23/02/03 – 26/02/03	UNTH
March 2003	02/03/03 – 05/03/03	UPTH
"	10/03/03 – 14/03/03	UBTH
"	17/03/03 – 19/03/03	NAUTH
"	23/03/03 – 26/03/03	UNTH
April 2003	30/03/03 – 02/04/03	UPTH
"	07/04/03 – 11/04/03	UBTH
"	14/04/03 – 17/04/03	NAUTH
"	20/04/03 – 23/04/03	UNTH
"	27/04/03 – 30/04/03	UPTH
May 2003	05/05/03 – 09/05/03	UBTH
"	12/05/03 – 14/05/03	NAUTH
"	18/05/03 – 21/05/03	UNTH
"	25/05/03 – 28/05/03	UPTH
June 2003	02/06/03 – 06/06/03	UBTH
"	09/06/03 – 11/06/03	NAUTH
"	15/06/03 – 18/06/03	UNTH
"	22/06/03 – 25/06/03	UPTH
July 2003	30/06/03 – 04/07/03	UBTH
"	07/07/03 – 09/07/03	NAUTH
"	13/07/03 – 16/07/03	UNTH

As shown above, each month I have traveled to each site to recruit cases and controls for the study. Consent, data collection, and biological sample collection procedures have been conducted according to the proposed protocol.

During this first year, the training component of this award has focused on acquiring the necessary skills to conduct epidemiology field work. During July, August 2002, my mentor, Dr. Clareann Bunker, and I met regularly regarding all of the details of supply ordering, plans for obtaining generator and freezer in Nigeria, informed consent, recruitment, refinement of data collection tools, data collection procedures, biological sample collection, biological sample aliquotting and storage, and biological sample shipment. In addition, I undertook University of Pittsburgh training courses in biohazard management, and in procedures and regulations governing the shipment of biological specimens. Since my arrival in Nigeria, I have consulted regularly with my mentor via e-mail.

Unexpected Difficulties.

1. Though the period of performance started July 1, 2002, the final letter of award was not received until July 24, 2002. As a result of the delay in receiving the funds, setting up the accounts, securing the travel advance for purchase of the generator, freezer, petrol, and travel expenses, I was unable travel to Nigeria to begin work until September, 2002.

2. The recruitment of study participants in Nigeria has not progressed as fast as expected as a result of certain unforeseen circumstances that arose in the course of the study. One major problem encountered in the past seven months is the issue of fuel scarcity in Nigeria. We needed to be able to purchase petrol in containers to be able to run the generator for steady power supply to keep the biological specimens frozen. At this time, a ban was placed on sale of petrol in containers. Although I made effort to obtain permission from Edo State Petroleum Task Force, the fuel stations were still reluctant to assist for fear of being closed down by security agents. The only option is to purchase the fuel with a car and siphon it into the generator. At very difficult periods, I have to purchase fuel at very exorbitant prices from local fuel vendors. The fuel scarcity also created difficulties in my traveling to the various study sites in Nigeria. More recently, there was a general strike in Nigeria for about 10 days during which period we were unable to recruit study participants. All these problems contributed to slowing down the rate of recruitment of study participants. Nevertheless, the study has progressed steadily over the past 12 months.

Deviation from Original Statement of Work.

As a result of the delays cited above, we were 3 months late in completing Task 1, Information Dissemination (and Study Startup), and we will be about 3 months late in completing Task 2, Data Collection. However, we expect to be able to accomplish Task 3, Laboratory Work, in less time than projected, and to be able to finish the project on time.

Key Research Accomplishment

- 141 Nigerian breast cancer cases and 71 age matched controls recruited; consent, questionnaires, physical measurements, and biological samples collected and stored.

Reportable Outcome

- Okobia MN. Molecular epidemiology of breast cancer – a review. (submitted manuscript, African Journal of Reproductive Health)

Conclusions

The target sample size for the study is 500 study participants (250 cases and 250 controls). Within the past six months, we have been able to recruit 212 study participants (141 cases and 71 controls). We believe that we will be able to meet the projected target study population within the next 10 months (between now and April, 2004). This will allow us eight months (May to December 2004) for laboratory studies (genotyping) at the University of Pittsburgh and six months (January to June 2005) for writing of reports and final presentation of research findings.

References (none)**Appendices (none)**